REMARKS

It is respectfully requested that the above amendments be entered under the provisions of 37 C.F.R. §1.116(b); that this application be reconsidered in view of the above amendments; and that all of the claims remaining in this application be allowed.

Amendments

As kindly noted by the Examiner, Applicants have requested amendments to Claims 16 and 18 to correct erroneous language contained therein. Specifically, the amendment to Claim 16 involves merely employing R6' consistently throughout this claim (as this term was employed in originally presented Claim 16); whereas the amendment requested to Claim 18 involves deletion of the objected to phrase "such as that".

In addition, Applicants have requested that Claims 1, 2 and 16 be amended to recite that R^2 and R^3 together with the nitrogen atom bound to R^2 and the carbon atom bound to R^3 form a heterocyclic or a substituted heterocyclic group selected from the group consisting of thiazolidinyl, piperidinyl and pyrrolidinyl wherein said substituted heterocylcic group contains from 1 to 2 substituents selected from the group consisting of fluoro, methyl, hydroxyl, amino, phenyl, thiophenyl and thiobenzyl. These amendments are supported by Applicants' specification at, for example, page 11, lines 15-29.

Each of the above amendments either place the claims in better form for appeal or comply with matters of form requested in the final Office Action. Entry of these amendments under the provisions of 37 C.F.R. §1.116(b) is earnestly solicited.

The requested amendments have been made in accordance with 37 C.F.R. §1.121 as amended on November 7, 2000. As required, attached hereto is an appendix illustrating the changes requested to Claims 16 and 18.

In view of the above, Claims 1-4, 7, 10, 12-13 and 15-22 remain in this application.

Rejection of Claims Under 35 U.S.C. §112, Second Paragraph

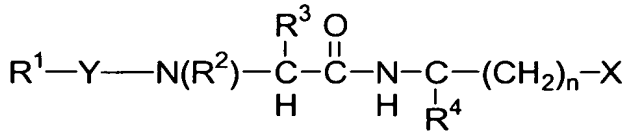
Claims 16 and 18 stand rejected under 35 U.S.C. §112, second paragraph, for the reasons set forth in the final Office Action. Applicants submit that this rejection has been obviated by the amendments to Claims 16 and 18 requested above. Withdrawal of this rejection is earnestly solicited.

Rejection of Claims Under 35 U.S.C. §103(a)

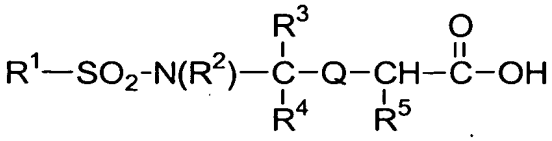
Claims 1-4, 7, 10, 12-13 and 15-22 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Adams, et al., International Patent Application Publication No. WO 96/22966. For the following reasons this rejection is traversed.

The test for non-obviousness articulated by the Court of Appeals for the Federal Circuit in *In re Vaeck* requires consideration of two factors: (1) whether the prior art would have suggested to those of ordinary skill in the art that they should practice the claimed invention; and (2) whether the prior art would also have provide a reasonable expectation of success to such a skilled artisan. *In re Vaeck*, 947 F.2d 488, 20 U.S.P.Q.2d 1438 (Fed. Cir. 1991).

The apparent premise of this rejection is two fold. First, the compounds disclosed by Adams, et al. are related to those now claimed by replacement of a hydrogen atom with a non-hydrogen substituent at the alpha amino acid position as set forth below:



(I, WO 96/22966)



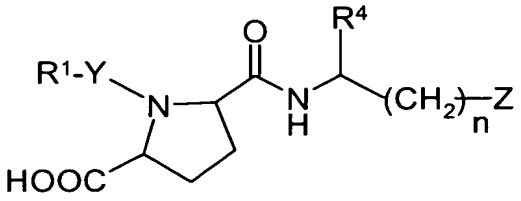
(I, instant application)

wherein, in Formula I of the instant application, neither R^3 nor R^4 is hydrogen.

Second, the replacement of a hydrogen atom with, e.g., a methyl group is not deemed to be patentably distinct absent evidence of superior or unexpected properties and, accordingly, the claimed invention is *prima facie* obvious over Adams, et al.

Applicants disagree with the above. Specifically, as now presented, the claimed invention is directed to R^2 and R^3 groups which, together with the nitrogen atom bound to R^2 and the carbon atom bound to R^3, form a heterocyclic or a substituted heterocyclic group selected from the group consisting of thiazolidinyl, piperidinyl and pyrrolidinyl wherein said substituted heterocylcic group contains from 1 to 2 substituents selected from the group consisting of fluoro, methyl, hydroxyl, amino, phenyl, thiophenyl and thiobenzyl. Each of these groups is a saturated heterocyclic group, i.e., one which contains no internal double bonds.

Contrarily, while Adams, et al. recite that his R^2 and R^3 groups can form a heterocyclic group, this group is defined by Adams, et al. as an unsaturated group. See, for example, page 12, lines 20-25. At best, Adams, et al. recite that as particular species, R^2 and R^3 can form a proline, azetidine or pipercolinic ring.[1] However, none of these rings are recited in the now claimed invention. For example, if R^2 and R^3 form a proline ring, as per Adams, et al., such a ring would provide for a compound of the structure:



Such a proline group is a carboxyl substituted pyrrolindyl group which is not included within the substituted heterocycles of the now claimed invention.

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[1]See, for example, page 21, line 19, to page 22, line 19, of Adams, et al.

In view of the above, Applicants maintain that Adams, et al. fail to teach or suggest the specific heterocyclic or substituted heterocyclic groups found in the now claimed invention. Absent such teaching or suggestion, this rejection is in error.

In addition to the above, Applicants take issue with the assertion that the substitution of hydrogen with, e.g., a methyl group creates a *prima facie* case of obviousness. Initially, such an assertion rings of an argument based on "homology". However, the mere fact that there is "homology" should not automatically be equated with *prima facie* obviousness. *In re Coes*, 81 U.S.P.Q. 369 (CCPA 1949); *In re Langer*, 175 U.S.P.Q. 169 (CCPA 1972). There must nevertheless be some motivation provided in the art to make the requisite compound. *In re Lalu*, 223 U.S.P.Q. 1257 (Fed. Cir. 1984).

Second, Applicants takes issue with any assertion that one skilled in the art would be motivated to replace the residue of a mono-α-substituted amino acid such as those employed by Adams, et al. and characterized by the $-N(R^2)CH(R^3)C(O)-$ group with the residue of a di-α,α-disubstituted amino acid as found in the claimed invention and characterized by the $-N(R^2)CR^3R^4C(O)-$ group. Applicants submit that no basis has been asserted in the Office Action that the skilled artisan would be motivated to make this replacement.

Third, this argument would be more germane if the explicit compounds disclosed by Adams, et al. were identical but for the specific modification noted above for the amino acid residue. However, this is simply not the case. For example, in order to arrive at compounds similar to those now claimed[2] from Adams, et al., it is necessary to first select Y to be $-SO_2-$ in the formula provided above, it is further necessary to select *n* to be zero and then to appropriately select X from the recited groups. Nothing in the final Office

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[2] As noted above, because of the specific recitations for the heterocyclic groups formed from R^2 and R^3 together with the nitrogen atom and carbon atom bound thereto respectively in the now claimed invention, even with the appropriate selection of other substituents, the compounds of Adams, et al. cannot fully read on those now claimed.

Action illustrates why the skilled artisan would be motivated to make such a selection. At best, Adams, et al. disclose a single compound with the appropriate Y group (compound 1013 at page 24 of Adams, et al.). However, this compound does not employ an R^2/R^3 heterocyclic group let alone a heterocyclic group as now claimed and, moreover, it employs an $n = 1$ variant as opposed to an $n = 0$ variant.

Lastly and for the sake of completion, Applicants submit that citation of *In re Lamberti and Konort*, 192 U.S.P.Q. 278 (CCPA 1976); *In re Wood, Whittaker, Stirling and Ohta,* 199 U.S.P.Q. 137 (CCPA 1978); and *In re Lohr and Spurlin,* 137 U.S.P.Q. 548 (CCPA 1963) in the Office Action is in error as it relates to the now claimed invention.

Specifically, in *In re Lamberti and Konort*, supra., the court explicitly stated that the cited art generically encompassed the compounds claimed by Lamberti and Konort and that there was an implicit suggestion in the art to modify their teachings to arrive at the specific compounds. See, for example, page 280 in the paragraph immediately after "Opinion".

Contrarily, the cited art in this case does not generically encompass the claimed compounds nor has the Examiner cited any basis in Adams, et al. as providing motivation to modify their teachings to arrive at the now claimed compounds. Accordingly, *In re Lamberti and Konort*, supra. is not germane to the issues in this application.

Likewise, in *In re Wood, Whittaker, Stirling and Ohta,* supra, and in *In re Lohr and Spurlin,* supra., the compounds of the cited prior art were otherwise identical to the claimed compounds but for the substitution of a dialkyl or spiro group at the 7 position of the pteridine ring[3] in Wood et al. or 2,6-dimethyl substitution of the thiomorpholine group in Lohr et al. However, such is not the case here since, as noted above, there is additional

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[3] In making this statement, Applicants note, as apparently did the Court, that the tautomeric structure depicted at positions 3 and 4 of Wood, et al.'s claimed invention is identical to that of the prior art.

significant selection of relevant substituents such as X, Y and *n* required to the Adams, et al. disclosure in order to arrive at similar structures to the now claimed invention.

Accordingly, Applicants submit that citation to this case law is not germane to the issues raised by Adams, et al. relative to the claimed invention.

Provisional Rejection Under Obviousness-Type Double Patenting

Claims 1-4, 7, 10, 12-13 and 15-22 stand provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims of copending Application No. 09/126,095. As this is a provisional rejection, it is not necessary for Applicants to traverse, obviate or render moot the rejection. Applicants do note, however, their disagreement with the Examiner's provisional finding.

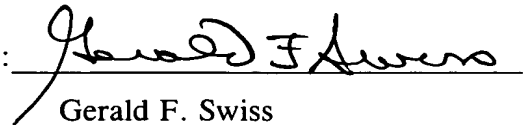
Conclusion

In view of the above amendments and remarks, Applicants submit that the instant application is now in condition for allowance, and a notice to that effect is respectfully requested. In the event that a telephone conference could expedite prosecution of the instant application, the Examiner is encouraged to contact the undersigned attorney for Applicants.

In order to avoid unintended abandonment of this application, a Notice of Appeal is enclosed.

Respectfully submitted,

Burns, Doane, Swecker & Mathis, L.L.P.

By: 

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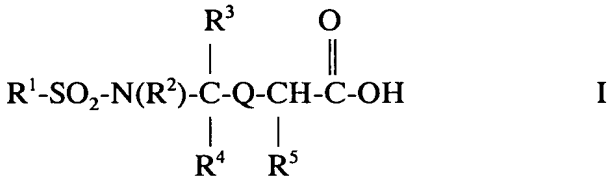
Date: December 4, 2001

Attachment to Reply and Amendment dated December 4, 2001

Marked-up Copy

Claims 1, 2, 16 and 18 were amended as follows:

--1. (twice amended) A compound of formula I:



I

where

R^1 is selected from the group consisting of alkyl, substituted alkyl, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, heterocyclic, substituted heterocylic, heteroaryl and substituted heteroaryl;

R^2 and R^3 together with the nitrogen atom bound to R^2 and the carbon atom bound to R^3 form a heterocyclic or a substituted heterocyclic group selected from the group consisting of thiazolidinyl, piperidinyl and pyrrolidinyl wherein said substituted heterocylcic group contains from 1 to 2 substituents selected from the group consisting of fluoro, methyl, hydroxyl, amino, phenyl, thiophenyl and thiobenzyl;

R^4 is selected from the group consisting of alkyl, substituted alkyl, aryl, substituted aryl, heteroaryl, and substituted heteroaryl;

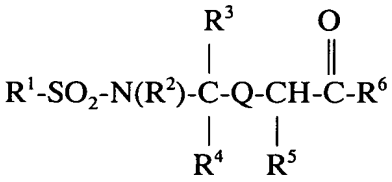
R^5 is selected from the group consisting of isopropyl, $-CH_2X$ and $=CH-X$ where X is selected from the group consisting of hydrogen, hydroxyl, acylamino, alkyl, alkoxy, aryloxy, aryl, aryloxyaryl, carboxyl, carboxylalkyl, carboxyl-substituted alkyl, carboxyl-cycloalkyl, carboxyl-substituted cycloalkyl, carboxylaryl, carboxyl-substituted aryl, carboxylheteroaryl, carboxyl-substituted heteroaryl, carboxylheterocyclic, carboxyl-

substituted heterocyclic, cycloalkyl, substituted alkyl, substituted alkoxy, substituted aryl, substituted aryloxy, substituted aryloxyaryl, substituted cycloalkyl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic with the proviso that when R^5 is =CH-X then (H) is removed from the formula and X is not hydroxyl;

Q is -C(X)NR^7- wherein R^7 is selected from the group consisting of hydrogen and alkyl; and X is selected from the group consisting of oxygen and sulfur;

or pharmaceutically acceptable salts thereof.

2. (twice amended) A compound of formula IA below:



IA

where

R^1 is selected from the group consisting of alkyl, substituted alkyl, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, heterocyclic, substituted heterocylic, heteroaryl and substituted heteroaryl;

R^2 and R^3 together with the nitrogen atom bound to R^2 and the carbon atom bound to R^3 form a heterocyclic or a substituted heterocyclic group selected from the group consisting of thiazolidinyl, piperidinyl and pyrrolidinyl wherein said substituted heterocylcic group contains from 1 to 2 substituents selected from the group consisting of fluoro, methyl, hydroxyl, amino, phenyl, thiophenyl and thiobenzyl;

R^4 is selected from the group consisting of alkyl, substituted alkyl, aryl, substituted aryl, heteroaryl, and substituted heteroaryl;

R^5 is selected from the group consisting of isopropyl, -CH_2X and =CH-X where X is selected from the group consisting of hydrogen, hydroxyl, acylamino, alkyl, alkoxy, aryloxy, aryl, aryloxyaryl, carboxyl, carboxylalkyl, carboxyl-substituted alkyl, carboxyl-cycloalkyl, carboxyl-substituted cycloalkyl, carboxylaryl, carboxyl-substituted aryl,

carboxylheteroaryl, carboxyl-substituted heteroaryl, carboxylheterocyclic, carboxyl-substituted heterocyclic, cycloalkyl, substituted alkyl, substituted alkoxy, substituted aryl, substituted aryloxy, substituted aryloxyaryl, substituted cycloalkyl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic with the proviso that when R^5 is =CH-X then (H) is removed from the formula and X is not hydroxyl;

R^6 is selected from the group consisting of amino, alkoxy, substituted alkoxy, cycloalkoxy, substituted cycloalkoxy, -O-(N-succinimidyl), -NH-adamantyl, -O-cholest-5-en-3-β-yl, -NHOY where Y is hydrogen, alkyl, substituted alkyl, aryl, or substituted aryl, $-NH(CH_2)_pCOOY$ where *p* is an integer of from 1 to 8 and Y is as defined above, $-OCH_2NR^9R^{10}$ where R^9 is selected from the group consisting of -C(O)-aryl and -C(O)-substituted aryl and R^{10} is selected from the group consisting of hydrogen and $-CH_2COOR^{11}$ where R^{11} is alkyl, and $-NHSO_2Z$ where Z is alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic or substituted heterocyclic;

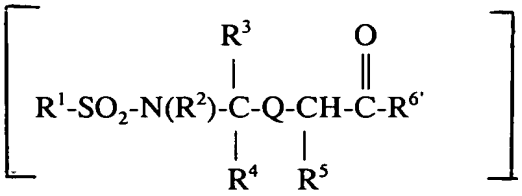
Q is $-C(X)NR^7-$ wherein R^7 is selected from the group consisting of hydrogen and alkyl; and X is selected from the group consisting of oxygen and sulfur;

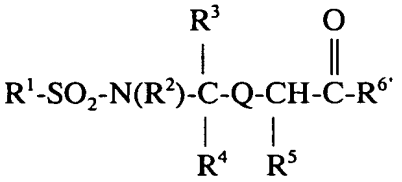
or pharmaceutically acceptable salts thereof

with the proviso that

when R^1 is *p*-methylphenyl, R^2 and R^3 are joined together with the nitrogen atom pendent to R^2 and the carbon atom pendent to R^3 to form a pyrrolidinyl ring, R^4 is methyl, R^5 is *p*-hydroxybenzyl then R^6 is not *t*-butoxy.

16. (twice amended) A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of a compound of the formula:





where

R^1 is selected from the group consisting of alkyl, substituted alkyl, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, heterocyclic, substituted heterocylic, heteroaryl and substituted heteroaryl;

R^2 and R^3 together with the nitrogen atom bound to R^2 and the carbon atom bound to R^3 form a heterocyclic or a substituted heterocyclic group selected from the group consisting of thiazolidinyl, piperidinyl and pyrrolidinyl wherein said substituted heterocylcic group contains from 1 to 2 substituents selected from the group consisting of fluoro, methyl, hydroxyl, amino, phenyl, thiophenyl and thiobenzyl;

R^4 is selected from the group consisting of alkyl, substituted alkyl, aryl, substituted aryl, heteroaryl, and substituted heteroaryl;

R^5 is selected from the group consisting of isopropyl, $-CH_2X$ and $=CH-X$ where X is selected from the group consisting of hydrogen, hydroxyl, acylamino, alkyl, alkoxy, aryloxy, aryl, aryloxyaryl, carboxyl, carboxylalkyl, carboxyl-substituted alkyl, carboxyl-cycloalkyl, carboxyl-substituted cycloalkyl, carboxylaryl, carboxyl-substituted aryl, carboxylheteroaryl, carboxyl-substituted heteroaryl, carboxylheterocyclic, carboxyl-substituted heterocyclic, cycloalkyl, substituted alkyl, substituted alkoxy, substituted aryl, substituted aryloxy, substituted aryloxyaryl, substituted cycloalkyl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic with the proviso that when R^5 is $=CH-X$ then (H) is removed from the formula and X is not hydroxyl;

[$R^{6'}$] R^6 is selected from the group consisting of 2,4-dioxo-tetrahydrofuran-3-yl (3,4-enol), hydroxyl, amino, alkoxy, substituted alkoxy, cycloalkoxy, substituted cycloalkoxy,

-O-(N-succinimidyl), -NH-adamantyl, -O-cholest-5-en-3-β-yl, -NHOY where Y is hydrogen, alkyl, substituted alkyl, aryl, or substituted aryl, $-NH(CH_2)_pCOOY$ where *p* is an integer of from 1 to 8 and Y is as defined above, $-OCH_2NR^9R^{10}$ where R^9 is selected from the group consisting of -C(O)-aryl and -C(O)-substituted aryl and R^{10} is selected from the group consisting of hydrogen and $-CH_2COOR^{11}$ where R^{11} is alkyl, and $-NHSO_2Z$ where Z is alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic or substituted heterocyclic;

Q is $-C(X)NR^7-$ wherein R^7 is selected from the group consisting of hydrogen and alkyl; and X is selected from the group consisting of oxygen and sulfur;

or pharmaceutically acceptable salts thereof

with the proviso that

when R^1 is *p*-methylphenyl, R^2 and R^3 are joined together with the nitrogen atom pendent to R^2 and the carbon atom pendent to R^3 to form a pyrrolidinyl ring, R^4 is methyl, R^5 is *p*-hydroxybenzyl then $R^{6'}$ is not *t*-butoxy.

18. (twice amended) The method according to Claim 17 wherein said inflammatory disease is selected from the group consisting of asthma, Alzheimer's disease, atherosclerosis, AIDS dementia, diabetes, inflammatory bowel disease, multiple sclerosis, rheumatoid arthritis, tissue transplantation, tumor metastasis, meningitis, encephalitis, cerebral traumas, nephritis, retinitis, atopic dermatitis, psoriasis, myocardial ischemia and acute leukocyte-mediated lung injury [such as that] which occurs in adult respiratory distress syndrome.--